Figure 1.1. Classical omega-3 and omega-6 fatty acid synthesis pathways and the role of omega-3 fatty acid in regulating health/disease markers.

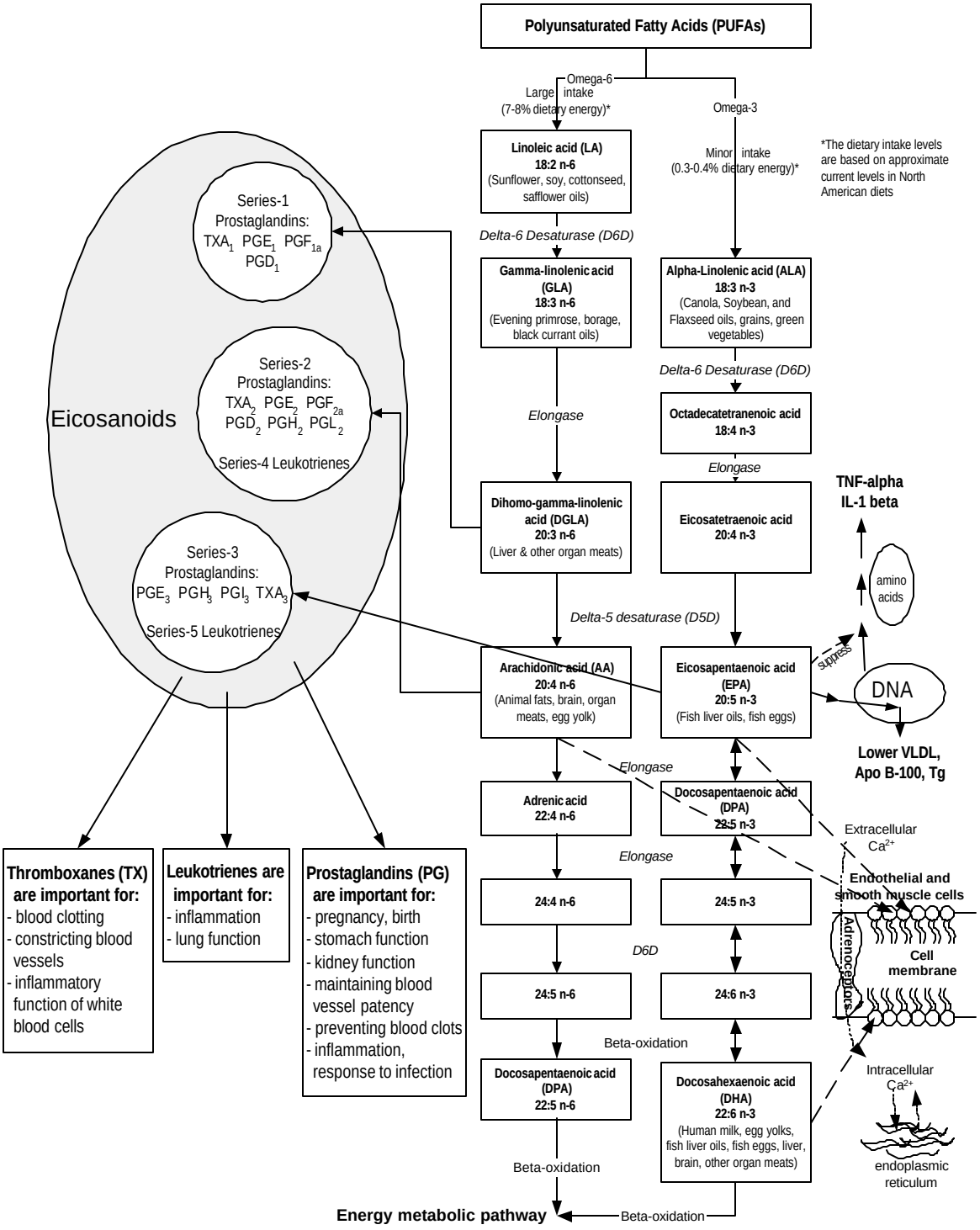
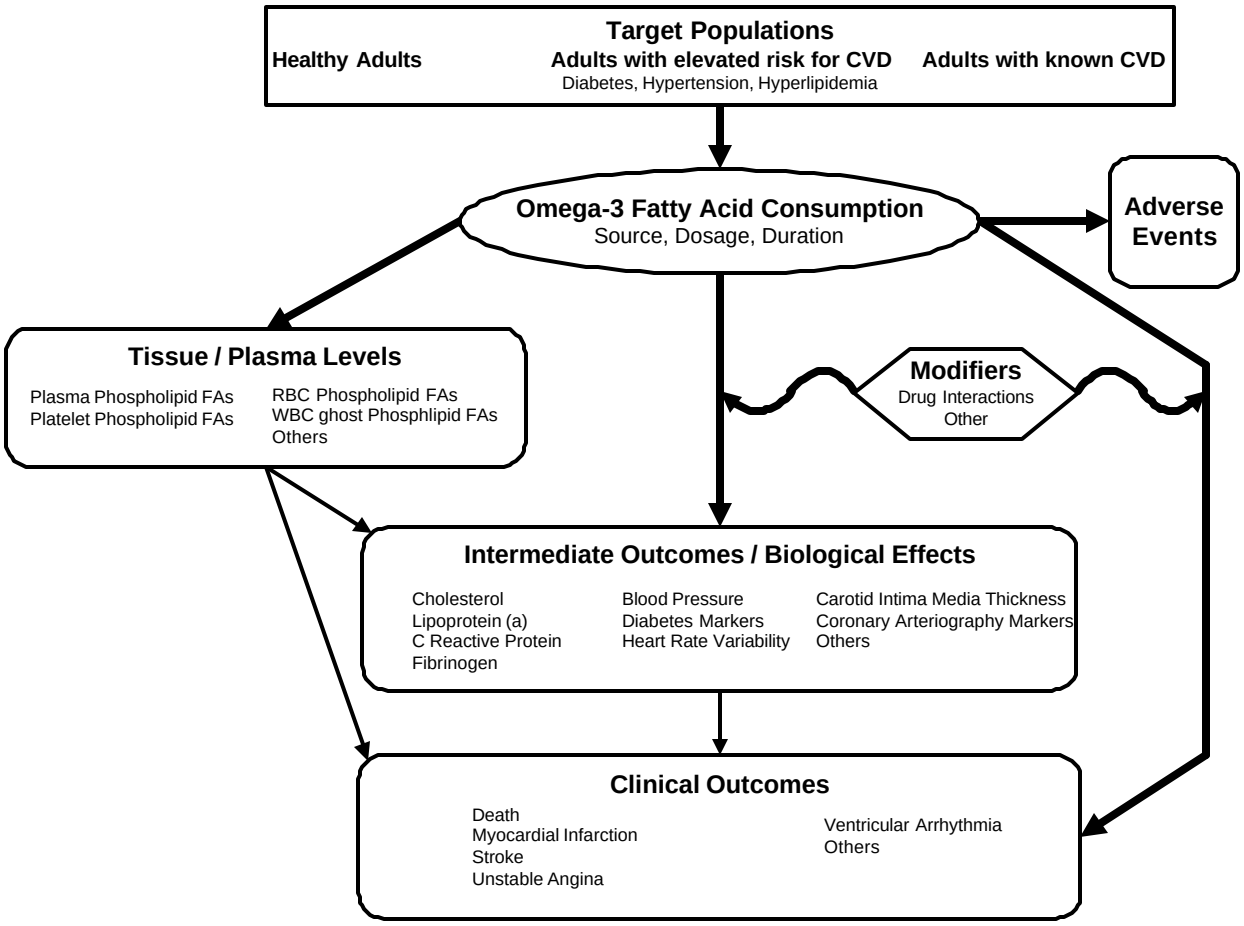


Figure 1.2. Analytic framework for omega-3 fatty acid exposure and cardiovascular disease. This framework concerns the effect of omega-3 fatty acid exposure (as a supplement or from food sources) on cardiovascular disease. Populations of interest are noted in the top rectangle, exposure in the oval, outcomes in the rounded rectangles, and effect modifiers in the hexagon. Thick connecting lines indicate associations and effects reviewed in this and the accompanying report. Lists noted in a smaller font indicate the specific factors reviewed. CVD indicates cardiovascular disease; FA, fatty acid; RBC, red blood cell (erythrocyte); WBC, white blood cell (leukocyte).

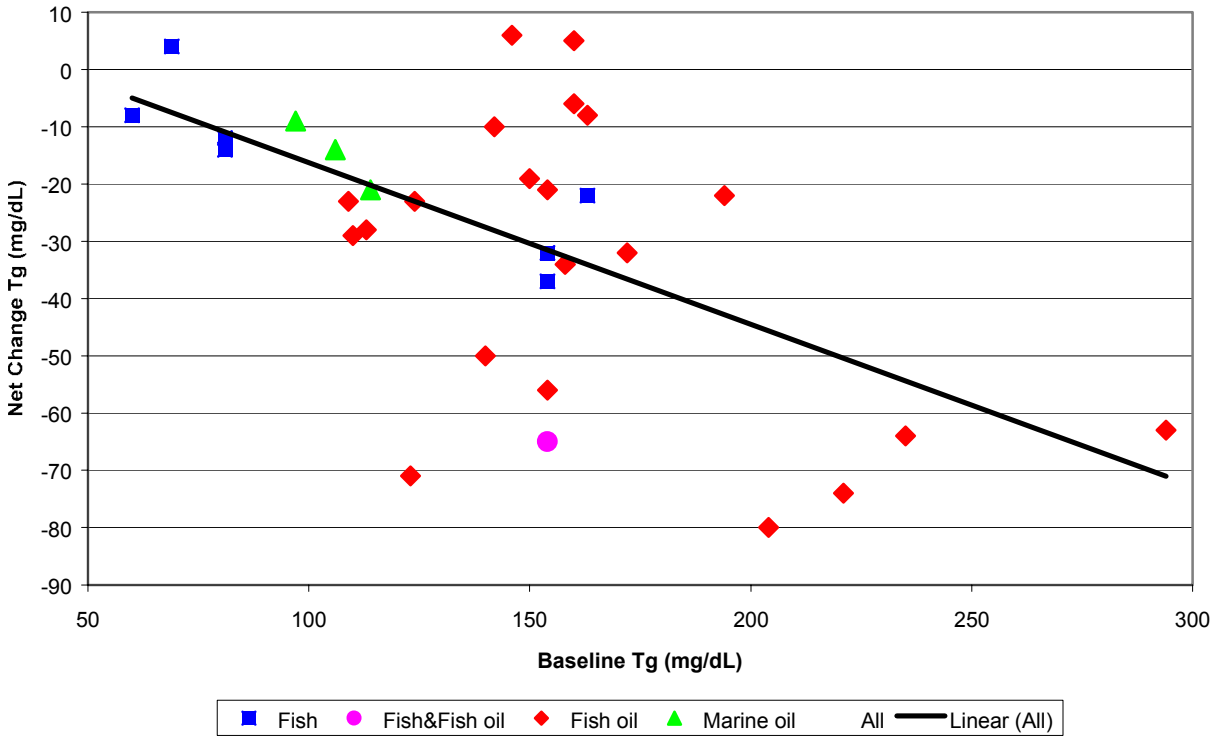


report. Once it is understood how to best estimate body stores of omega-3 fatty acids, it will then be of interest in future reviews to understand how levels of body stores affect cardiovascular outcomes.

Although the most important questions relating to omega-3 fatty acids pertain to their effects on clinical outcomes (and potential adverse events), collecting data on long-term cardiovascular effects is relatively difficult. As a result, the bulk of the available evidence generally pertains to the efficacy in trials of interventions on intermediate outcomes and biological effects. This evidence is summarized in this report.

The effects of omega-3 fatty acids on CVD risk factors, intermediate markers of CVD and clinical outcomes can be related to one another in two ways. First, by reducing risk factors for CVD, such as blood pressure, or putative markers of the risk factors, such as C-reactive protein, omega-3 fatty acids can directly reduce the overall risk of cardiovascular events. Second, omega-3 fatty acids can have a direct or indirect beneficial effect on specific intermediate markers of

Figure 3.1 Meta-regression of baseline triglyceride (Tg) level versus net change in Tg. Each point represents an individual study or study arm. Marine oils include non-fish animal sources including Minke whale and seal. Regression not adjusted for dose of omega-3 fatty acid or study size.

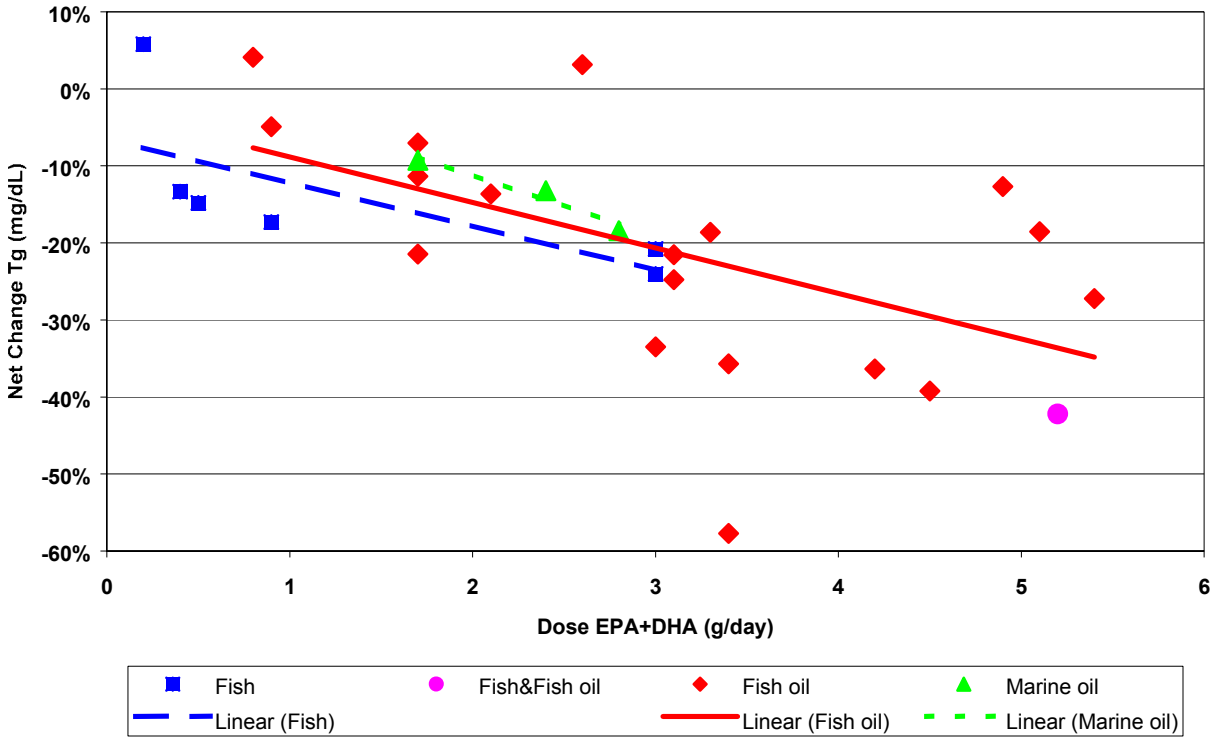


Dose and Source Effect

The 4 studies that compared different doses of marine oil supplements found that the greatest net decrease in Tg level occurred in study arms receiving the highest dose of EPA+DHA, although none of the articles reported whether there was a significant trend within the study. Across studies there was a clear trend toward greater percent decrease in Tg with higher doses, regardless of source (Figure 3.2). At least a 10% reduction in Tg was found in most studies with doses of at least 1.7 g per day of marine oil supplementation. Most study arms with doses of at least 3 g per day of marine oil supplements resulted in at least a 20% reduction in Tg. Among the studies of dietary fish, only the 2 arms with high omega-3 fatty acid fish diets in Mori, et al. achieved at least a 20% reduction of Tg [71].

Grimsgaard et al., overall, found no difference in effect between purified EPA and purified DHA, although the net decreases in Tg were consistently greater in the DHA group than in the EPA group across quartiles of baseline Tg [66]. Across studies, and within the Mori et al. study [71], the source of the EPA+DHA, whether as a supplement or from dietary fish, does not appear to make a difference. In contrast, the effect of ALA is uncertain. The single study that evaluated pure ALA supplementation, Finnegan et al., found increases in Tg levels in subjects on both 4.5 g and 9.5 g per day of ALA margarine (the latter dose is not included in the summary table) [53]. Both Singh et al. and de Lorgeril et al. provided ALA in the context of a Mediterranean diet, which also included higher dietary fish intake [49,76].

Figure 3.2 Meta-regression of dose of EPA+DHA intake versus net change in triglycerides (Tg). Each point represents an individual study or study arm. Separate simple regressions were performed for each oil source type (except for the individual study arm of combined fish and fish oil). Marine oils include non-fish animal sources including Minke whale and seal. Regression not adjusted for baseline Tg or study size.



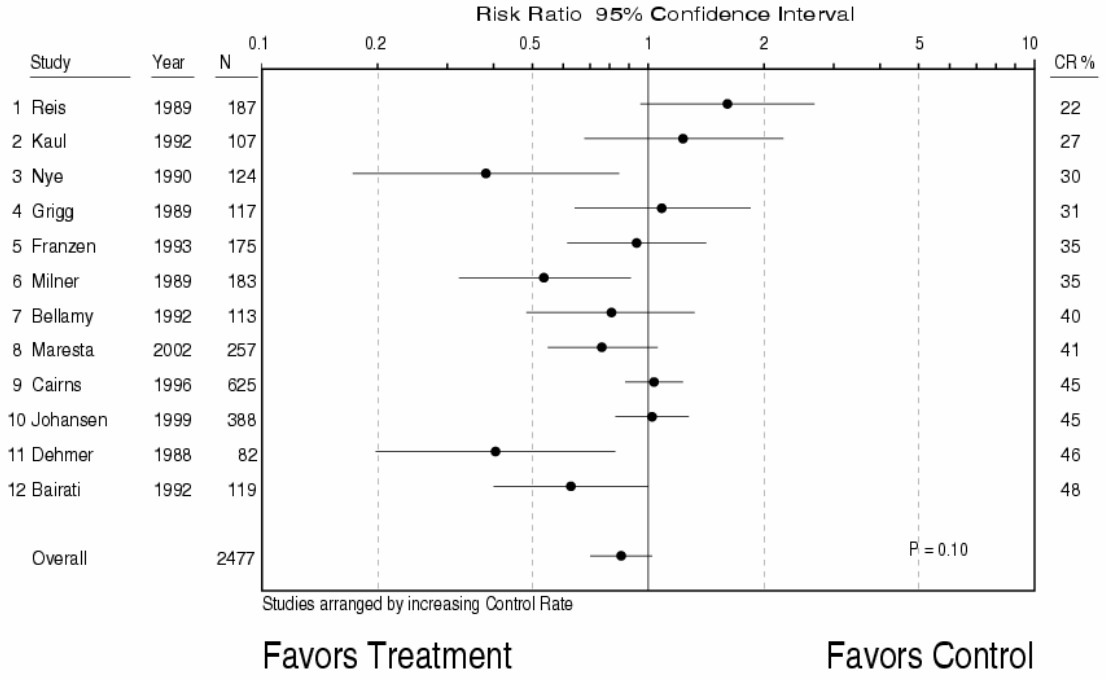
Exposure Duration

The effect of duration of intervention or exposure was somewhat inconsistent among the 4 studies that reported data on Tg levels at different time points in studies of omega-3 fatty acids. Hanninen et al. found progressive decreases of Tg at 5 and 12 weeks in group of subjects consuming higher amounts of fish [67]. Similarly, Nilsen et al found progressive decreases in men, but not in a small group of women, at 6 weeks, 6 months and 12 months [73]. Sirtori et al. found that the effect of lower dose fish oil supplementation to reduce Tg occurred by 2 months and remained stable at 4 and 6 months [77]. In contrast, Finnegan et al. reported a significant decrease (15%) in mean Tg levels after 2 months which was not sustained at 6 months in the EPA+DHA arms [53]. Across studies, there is no apparent correlation between study duration and fish oil supplement effect, even after grouping studies by fish oil dosage.

Sustainment of Effect

No study reported data on an effect after ceasing omega-3 fatty acid treatment.

Figure 3.3 Random effects model of effect of fish oil on coronary artery restenosis following percutaneous transluminal coronary angioplasty.



N = number of patients, except for 2 studies that reported number of lesions: Nye [168] had 35 patients on fish oil, 34 on control; Grigg [164] had 52 patients on fish oil, 56 on control. CR% = control rate, the restenosis rate in the control arm.

Table 3.31 Effect of omega-3 fatty acid supplementation on fatty acid profile of monocyte phospholipids in randomized trials (8 weeks)

Study, Year	Omega-3 Fatty Acid Arms [a] Control Arm N	Source	g/d	Base ED (%) [b]	Results (Δ%) [c] AA [f]	ALA	EPA	DHA	Quality [d] Summary	Jadad	Allocation Conceal	Applicability [e]
	EPA/DHA Oils											
Hansen, 1989	40 [g]	Cod liver oil	ED 5.8	nd	-4.00 [h]		+3.00 [h]		C	1	Un	GEN I
		No oil	ED 0	nd	nd		nd					

nd = no data

a A = ALA; D = DHA; E = EPA; ED = EPA+DHA; T = total omega-3 fatty acids.

b Baseline EPA + DHA profile (% of total fatty acids) of monocyte phospholipids.

c Δ% = Difference of the marker's profile (post-treatment minus pre-treatment).

d A = good quality; B = fair quality; C = poor quality; Jadad = Jadad Score (0-5, based on randomization, double blinding, and dropouts); Ad = adequate allocation concealment; In = inadequate allocation concealment; Un = allocation concealment unclear. See Methods.

e CVD = history of cardiovascular disease; DM I/II = diabetes mellitus type 1 or 2; DysLip = dyslipidemia; GEN = general, healthy population; N/IDDM = (non-) insulin dependent diabetes mellitus. I = broadly applicable; II = applicable to sub-group; III = narrow applicability. See Methods.

f Arachidonic acid (20:4 n-6)

g Cross-over study.

h Difference from the control after 8-week treatment. Assumed control's profile didn't change from baseline, so differences from the controls would be approximately equal to the Δ%.

Figure 3.4 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in plasma or serum phospholipids (PL)

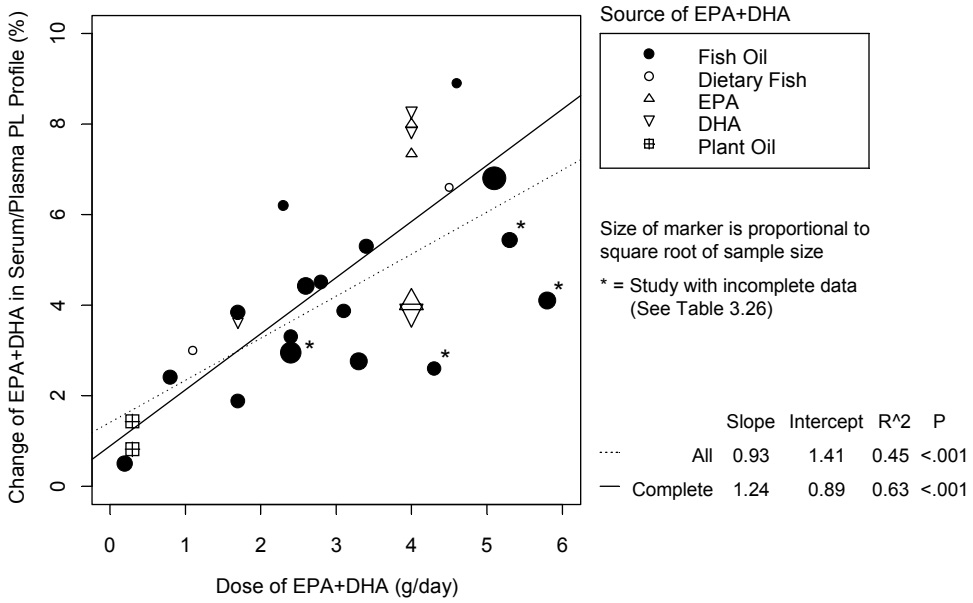


Figure 3.5 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in platelet phospholipids (PL)

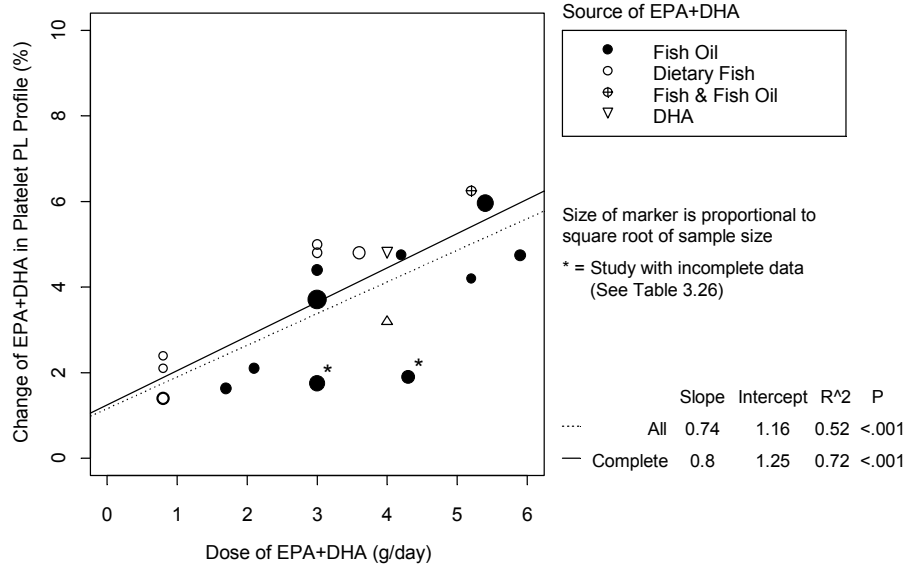


Figure 3.6 Association between EPA and/or DHA supplementation and changes in EPA+DHA composition in red blood cell (RBC, erythrocyte) membrane phospholipids (PL)